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Dkt. 0575/66602-B/JPW/BJA/CSA

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Silviu Itescu
U.S. Serial No. : 10/693,480 Group Art Unit:1647
Filed : October 23, 2003 Examiner: B. E. Bunner
For : REGENERATION OF ENDOGENOUS MYOCARDIAL
TISSUE

30 Rockefeller Plaza, 20th Fl.
New York, New York 10112
March 18, 2010

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

**COMMUNICATION IN RESPONSE TO SEPTEMBER 18, 2009 OFFICE ACTION AND
PETITION FOR A THREE-MONTH EXTENSION OF TIME AND
SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT**

This Communication is submitted in response to the September 18, 2009 Office Action issued by the United States Patent and Trademark Office in connection with the above-identified application. A response to the September 18, 2009 Office Action was due December 18, 2009. Applicant hereby petitions for a three-month extension of time. The fee for a three-month extension of time for a small entity is FIVE HUNDRED AND FIFTY FIVE DOLLARS (\$555.00), and a check including this amount is enclosed. With a three-month extension of time a response is now due March 18, 2010. Accordingly, this response is being timely filed.

Remarks start on page 2.

Supplemental Information Disclosure Statement starts on page 7.

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REMARKS

Claims 35, 37, 43, 46, 47, 49-51, and 57 are pending.

Obviousness-Type Double Patenting

The Examiner stated that claims 35, 37, 43, 46-47, 49, 50, 51 and 57 are provisionally rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 69, 77-78, and 82-84 of co-pending Application No. 11/234,879. The Examiner stated that although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to a method of treating a disorder comprising administering stromal-derived factor-1.

In response, applicant respectfully traverses the rejection. Applicant notes that U.S. Application No. 11/234,879, now U.S. Patent No. 7,662,392, discloses a method of increasing trafficking of bone marrow-derived endothelial progenitor cells to ischemic myocardium in a subject comprising administering to the subject an amount of Stromal-Derived Factor-1 (SDF-1) effective to attract bone marrow-derived endothelial progenitor cells to the ischemic myocardium. In contrast, the invention currently claimed in the subject application describes a method of treating a subject suffering from a disorder of a heart tissue involving loss or apoptosis of cardiomyocytes which comprises intramyocardially or intracoronarily administering to the subject an amount of an agent comprising a human stromal derived factor-1 effective to induce regeneration of endogenous cardiomyocytes.

Applicant notes that a method effecting regeneration of endogenous

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cardiomyocytes is not obvious over a method of increasing trafficking of bone marrow-derived endothelial progenitor cells to ischemic myocardium. The different cell types and the different mechanism of action recited in the present claims are not obvious over the claims of Patent No. 7,662,392.

Accordingly, applicant respectfully requests that the Examiner reconsider and withdraw this ground of rejection.

Claims Rejected Under 35 U.S.C. §103

The Examiner stated that claims 35, 37, 43, 46, 49-51 and 53-57 are rejected under 35 U.S.C. §103(a) as being unpatentable over Petersen, BE (U.S. 2002/0094327) in view of Hung et al. (U.S. 2003/0171294). The Examiner stated that Petersen teaches that modulating the level of SDF-1 α protein in a target tissue can selectively direct migration of pluripotent stem cells to the target tissue (page 1, [0006]). The Examiner stated that Petersen discloses that by "increasing the number of pluripotent stem cells that traffic to the target tissue, the rate of tissue repair can be increased because there will be a greater number of pluripotent stem cells in the target tissue that can differentiate into cells which can repopulate and partially or wholly restore the normal function of the damaged tissue" (page 1, [0006]). The Examiner stated that Petersen teaches that the heart is one of the target tissues within a mammalian subject in which SDF-1 α is administered (page 8, column 2, [0063]). The Examiner stated that although Petersen does not teach that SDF-1 α is administered to the heart intramyocardially or intracoronarily, Hung et al. teaches that it is routine to administer factors via intramyocardially and intracoronarily to the heart.

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The Examiner alleged that it would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the method of administering of SDF-1 α to heart tissue as taught by Petersen by utilizing intramyocardial or intracoronary administration as taught by Hung et al. The Examiner alleged that the person of ordinary skill in the art would have been motivated to make that modification in order to localize cell migration/differentiation and tissue repair (see for example, Hung et al. page 1, [0007]).

In response, applicant respectfully traverses the Examiner's rejection. Applicant submits that claim 35 recites "A method of treating a subject suffering from a disorder of a heart tissue involving loss or apoptosis of cardiomyocytes which comprises intramyocardially or intracoronarily administering to the subject an amount of an agent comprising a human stromal derived factor-1 effective to induce regeneration of endogenous cardiomyocytes and thereby treat the disorder of the heart tissue involving loss or apoptosis of cardiomyocytes in the subject." Applicant maintains that the combination of Hung et al. and Petersen does not teach such a method.

Petersen provides a laundry list of tissues to which SDF-1 α could theoretically be administered in order to effect trafficking of "a pluripotent stem cell" to the tissue "from another site" in the subject (e.g. see abstract and paragraph [0063] on page 8). In contrast, the method as currently claimed herein induces regeneration of endogenous cardiomyocytes in a specific tissue. There is no teaching of such a method in the combination of Petersen and Hung et al. The discussion in Petersen of

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repopulating a damaged tissue with pluripotent stem cells, as cited by the Examiner, is not a disclosure of regeneration of endogenous cells, less so endogenous cardiomyocytes.

Applicant also notes that there is nothing in Hung et al. to suggest administration of SDF-1 to the heart intramyocardially or intracoronarily.

Hung et al. describes two animal models of coronary artery disease, a hibernating myocardium model and an ameriod model:

Hibernating Myocardium Model

Hung et al. states that "[h]ibernating tissue is non-contracting muscle tissue, but is capable of contracting, should it be adequately resupplied with blood" (paragraph [0038]). Applicant notes that Hung et al. classifies heart muscle as "healthy, normal or dead" (paragraph [0038]). Hung et al. then distinguishes "dead or diseased heart tissue" from "hibernating tissue" (paragraph [0038]). Applicant's claimed invention, being directed to a "disorder of a heart tissue involving loss or apoptosis of cardiomyocytes" as recited in claim 35, is thus distinguished from the hibernating model. As such, the hibernating model does not correspond to applicant's claimed invention of treating a disorder of the heart. The data in Hung et al. showing administration of a polypeptide fibroblast growth factor (FGF) intramyocardially to the hibernating model is thus not relevant to subjects "suffering from a disorder of a heart tissue involving loss or apoptosis of cardiomyocytes," as recited in claim 35.

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Ameroid Model

Hung et al. also describes the ameroid model in which there is complete occlusion leading to infarction and states that "the 100% occlusion that is provided by the ameroid model makes the ameroid model more analogous to a myocardial infarction" (paragraph [0039]).

Administration of the polypeptide FGF to the ameroid model, however, provided no benefit over placebo (see Figures 7-9 of Hung et al.). Accordingly, Hung et al. shows that administration of FGF to a subject having a diseased heart provided no beneficial effect.

In view of this data present in Hung et al., a person of ordinary skill in the art would have no motivation to treat "a subject suffering from a disorder of a heart tissue involving loss or apoptosis of cardiomyocytes which comprises intramyocardially or intracoronarily administering to the subject an amount of an agent comprising a human stromal derived factor-1" because Hung et al. teaches away from intramyocardial or intracoronarial injection of a polypeptide to treat a subject suffering from a disorder of a heart tissue involving loss or apoptosis of cardiomyocytes.

Accordingly, applicant maintains that the claimed invention is not obvious over the combination of Petersen, BE in view of Hung et al., and respectfully requests that the Examiner reconsider and withdraw this ground of rejection.

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SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

In accordance with the duty of disclosure under 37 C.F.R. §1.56, applicant directs the Examiner's attention to the items listed below which are also listed on the Substitute PTO-1449 form attached hereto as **Exhibit A**. Copies of items 1-15 are enclosed herewith as **Exhibits 1-15**, respectively.

1. Berk, B. (2007), "Novel Approaches to Treat Oxidative Stress and Cardiovascular Disease," Trans. Am. Clin. Clim. Assoc., 118:209-214; (**Exhibit 1**)
2. Prosperi et al. (1993), "A Human cDNA Corresponding to a Gene Overexpressed during Cell Proliferation Encodes a Product Sharing Homology with Amoebic and Bacterial Proteins" J. Biol. Chem., 268(15):11050-11056; (**Exhibit 2**)
3. Smith, W. (1991), "Interleukin-8 induces Neutrophil Transendothelial Migration," Immunology 72:65-72; (**Exhibit 3**)
4. Takahashi et al. (1995) "Effects of Endothelial Interleukin-8 on Neutrophil Migration Across an Endothelial Monolayer," Cardiovasc Res 29:670-675; (**Exhibit 4**)
5. Kang et al. (1998) "Mammalian Peroxiredoxin Isoforms can Reduce Hydrogen Peroxide Generated in Response to Growth Factors and Tumor Necrosis Factor-Alpha," Journal of Biological Chemistry 273(11):6297-6302; (**Exhibit 5**)

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6. Zhang et al. (1997) "Thioredoxin Peroxidase in a Novel Inhibitor of Apoptosis with a Mechanism Distinct from that of BCL-2," Journal of Biological 272(49):30615-8; **(Exhibit 6)**
7. Berggren et al. (2001) "Thioredoxin Peroxidase-1 (Peroxioredoxin-1) is Increased in Thioredoxin-1 Transfected Cells and Results in Enhanced Protection Against Apoptosis Caused by Hydrogen Peroxide but not by other Agents Including Dexamethasone, Etoposide, and Doxorubicin" Archives of Biochemistry and Biophysics 392(1):103-9; **(Exhibit 7)**
8. Song et al. (2003) "Vitamin D3 Up-regulating Protein 1 (VDUP1) Antisense DNA Regulates Tumorigenicity and Melanogenesis of Murine Melanoma Cells via Regulating the Expression of Fas Ligand and Reactive Oxygen Species" Immunol Lett 86:235-247; **(Exhibit 8)**
9. Perrone et al. (2009) "Thioredoxin Interacting Protein (TXNIP) Induces Inflammation Chromatin Modification in Retinal Capillary Endothelial Cells under Diabetic Conditions" J Cell Physiol 221:262-272; **(Exhibit 9)**
10. Weber et al. (2000) "Fibrosis and Hypertensive Heart Disease" Curr Opin Cardiol 15:264-272; **(Exhibit 10)**
11. December 23, 2009 Final Office Action issued in connection with U.S. Serial No. 11/894,581;

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(Exhibit 11)

12. December 29, 2009 Final Office Action issued in connection with U.S. Serial No. 11/648,769;

(Exhibit 12)

13. January 28, 2010 Office Action issued in connection with U.S. Serial No. 10/512,518; **(Exhibit 13)**

14. Terui et al. (1998) "Activated Endothelial Cells Induce Apoptosis in Leukemic Cells by Endothelial Interleukin-8" Blood 92:2672-80; **(Exhibit 14)** and

15. Terui et al. (1999) "NH2-terminal Pentapeptide of Endothelial Interleukin 8 is Responsible for the Induction of Apoptosis in Leukemic Cells and has an Antitumor Effect in vivo" Cancer Research 59:5651-5. **(Exhibit 15)**

This Supplemental Information Disclosure Statement is being submitted under 37 C.F.R. §1.97(c)(2). Accordingly, applicant encloses a check in the amount of ONE HUNDRED AND EIGHTY DOLLARS (\$180.00) for filing this Supplemental Information Disclosure Statement.

The Examiner is respectfully requested to make the listed items of record in the present application by initialing and returning a copy of the enclosed Substitute Form PTO 1449.

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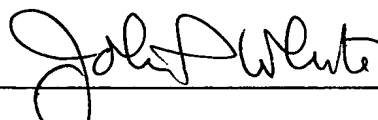
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If a telephone interview would be of assistance in advancing prosecution of the subject application, applicant's undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee, other than the total enclosed \$735.00 fee, including a \$555.00 fee for a three-month extension of time and a \$180.00 Information Disclosure Statement fee, is deemed necessary in connection with the filing of this Communication and Supplemental Information Disclosure Statement. However, if any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

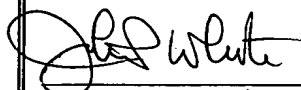
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3/18/10

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